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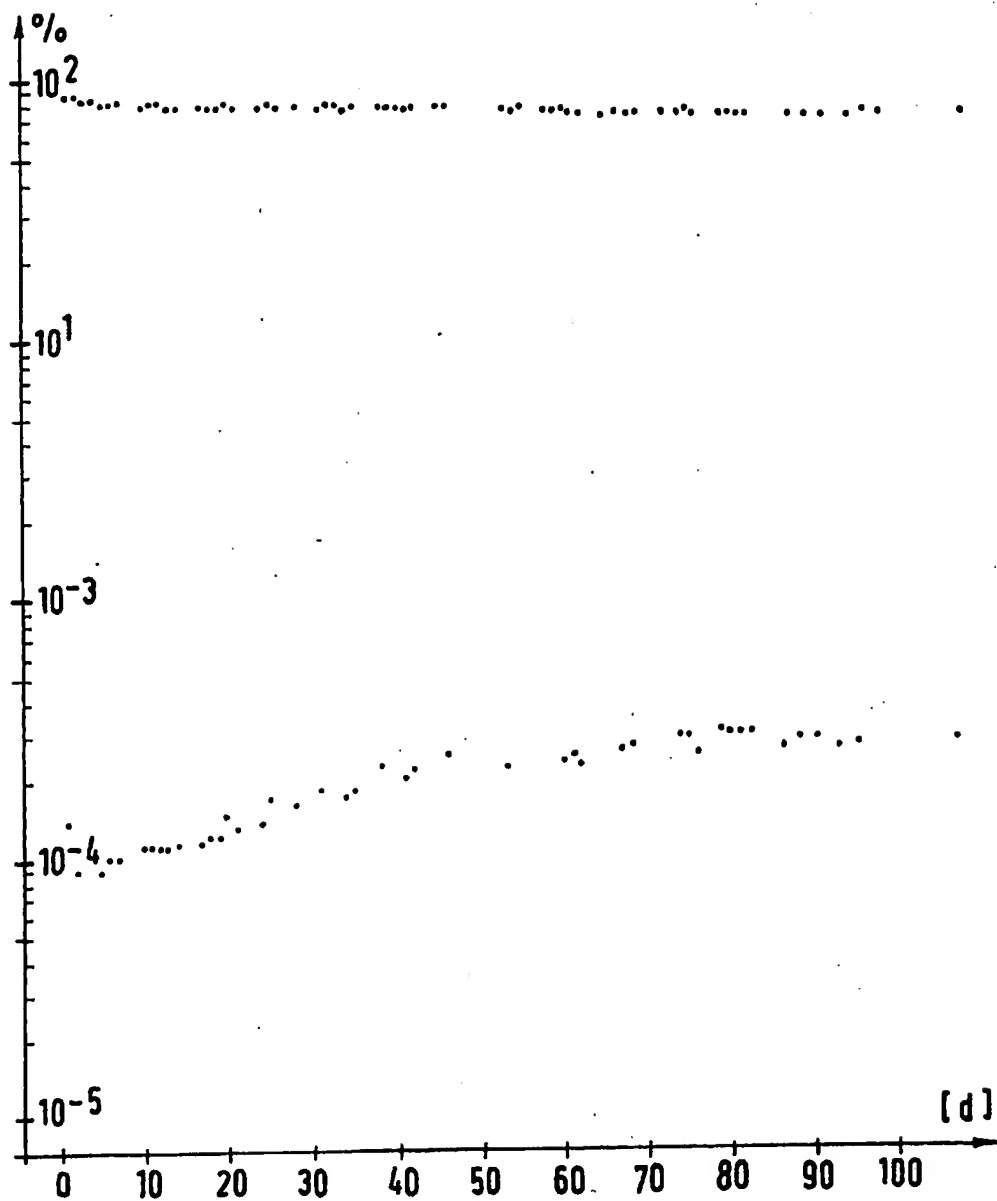
(54) Ion-exchanger for Separating
Gallium-68 from its Parent Nuclide
Germanium-68

(57) The ion exchanger consists
entirely or substantially of a
condensation product obtained from
polyhydroxybenzene having not less
than 2 adjacent hydroxyl groups
(ortho-position) and formaldehyde in a
molar excess of 5 to 15%, or contains
such a condensation product

Incorporated therein, wherein the
condensation product has a reversible
water content of not less than 40% by
weight. A process for preparing such
an ion-exchanger comprises reacting
in an inert medium (e.g. paraffin) 3.4
M pyrogallol with a 10% molar excess
of 37% aqueous formaldehyde
solution at 85—90°C, and pH 8 to
6.8. The product is cured at 115 to
120°C for 15 to 25 hours and then
the inert medium filtered off.

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SPECIFICATION

Ion-exchanger for Separating Gallium-68 from its Parent Nuclide Germanium-68, Processes for its Preparation and the Use Thereof

- The invention relates to an ion exchanger for separating gallium-68 from its parent nuclide germanium-68, the ion exchanger consisting entirely or substantially of a condensation product obtained from polyhydroxybenzene having not less than 2 adjacent hydroxyl groups (ortho-position) and formaldehyde in a molar excess of 5 to 15%, or containing such a condensation product incorporated therein, and the condensation product having a reversible moisture content of not less than 40% by weight.
- As is known, there is a need in nuclear medical diagnosis for the provision of gallium-68, which hitherto has been obtained by very diverse methods. Thus, for example, a generator with the aid of which germanium-68 is adsorbed on aluminium oxide, and gallium-68 is then eluted with EDTA, has been disclosed in Int. J. Appl. Rad. Isotopes Vol. 12, page 62 (1961); this generator is now available commercially. The process using this generator has the disadvantage that different yields of gallium-68 are obtained, these being between 30 and 70%, based on Ge-68, and that the Ga-68 obtained is in the form of a EDTA complex, which has to be destroyed before further processing to obtain radiopharmaceutical agents. For this reason, this process and the labelling of pharmaceutical agents with the Ga-68 thus obtained is very time-consuming and expensive.
- The adsorption of Ge-68 on antimony pentoxide has been disclosed in Int. J. Appl. Rad. Isotopes, Vol. 29, page 120 (1978), and in this case the elution of the Ga-68 is then carried out with sodium oxalate. With this procedure the proportion of Ge-68 in the Ga-68 eluate is too high, for example 0.05%, based on eluted Ga-68. In this case, the oxalate complex must be destroyed before further processing.
- The liquid extraction of Ga-68 with oxine/chloroform is described in J. Nucl. Med., Vol. 19, page 925 (1978). This process is time-consuming and demands precise working during the extraction, so that with this known process there is a danger of operator errors.
- For this reason, a Ge-68/Ga-68 nuclide generator, for ion exchange chromatography, from which Ga-68 can be eluted without the addition of chelating agents, for example with dilute mineral acids (preferably HCl since, after neutralisation, this does not have to be separated off from the solution of the pharmaceutical agent) is of interest.
- A number of polyhydroxybenzene-containing ion exchangers which are able to bond metal ions selectively from acid, aqueous solutions have been disclosed in the literature (British Patent Specification 806,871, German Offenlegungsschrift 2,128,802, Austrian Patent Specification 334,084, German Offenlegungsschrift 2,450,541, G. Cassidy J. Am. Chem. Soc., Vol. 71, No. 2, page 402 (1949) and G. V. Myasoedova et al. Zh. Analit. Khim. 23, No. 4, page 507 (1968)). However, only the pyrogallol/formaldehyde resin mentioned in the Russian literature reference and the condensation product of hydrolysable tanning agent concentrates and formaldehyde (hydrolysable tanning agent concentrates contain gallic acid, some of which is also converted to pyrogallol on curing at between 300 and 400°C) which is disclosed in Austrian Patent Specification 334,084, are suitable for adsorbing germanium from mineral acid solution.
- However, three demands must be made of such a pyrogallol/formaldehyde resin if it is to be used as a Ge-carrier in a Ge-68/Ga-68 nuclide generator:
1. The ion exchanger must have a high capacity for germanium (only a slight excess of formaldehyde may be used in the condensation reaction), so that it is possible to elute the generator 800—1,000 times without Ge-68 breaking through.
 2. The ion exchanger must have a reversible water content of $\geq 40\%$, so that an adequately rapid diffusion of the daughter nuclide Ga-68 from the resin particles, and thus a high yield, are ensured.
 3. The ion exchanger may have only an extremely low solubility in the eluate (this is achieved by subjecting the condensation product to long curing times), since otherwise it is necessary to subject the eluate to additional purification steps.
- However, these three demands are met to only an unsatisfactory extent by the ion exchangers disclosed in the literature, since, for example, the exchanger disclosed in the Russian publication has too low a capacity because of an unfavourable pyrogallol:formaldehyde ratio and, for example, the exchanger according to the Austrian Patent Specification 334,084 contains too little water, since no water is added apart from that in the formaldehyde solution and the diffusion of Ga-68 is thus greatly hindered. In the case of the known exchangers, the solubility also leaves something to be desired.
- An exchanger which satisfies the 3 said demands in all respects would therefore be highly desirable. This exchanger is the object of the invention.
- A complexing agent-free separation, which can be repeated as desired, of Ga-68 from its parent nuclide Ge-68 in high yield is made possible with the aid of an ion exchanger which can be loaded with the parent nuclide Ge-68 and, on elution, for example with dilute hydrochloric acid (preferably 2N—5N) releases Ga-68 in ionic form in high yield (of the order of magnitude of 75%) with a very low level of contamination by Ge-68 (of the order of magnitude of 0.0003%).
- To prepare the ion exchanger, a polyhydroxybenzene having not less than two adjacent hydroxyl

groups (ortho-position), for example pyrogallol, is subjected to a condensation reaction with formaldehyde, the formaldehyde being present in a slight molar excess of 5 to 15 mol % and preferably 10 mol %. Larger amounts of formaldehyde lower the exchanger capacity and smaller amounts result in an adverse increase in the solubility of the resin in water and acid. The use of a formaldehyde excess of 5 to 15% is thus fairly critical.

The condensation reaction is started by heating, and for this purpose the reaction mixture is appropriately introduced into a hot, hydrophobic medium which is inert towards the reactants and thus compatible with the latter; if pyrogallol is used, the hydrophobic medium is preferably heated to 85 to 90°C. The hydrophobic medium used is preferably viscous paraffin, which forms a suspension with the aqueous solution, small resin particles being pre-formed. Temperatures which are much higher are a disadvantage inasmuch as the reaction medium foams, especially if the boiling point of water is exceeded in the exothermic reaction. At much lower temperatures, the reaction proceeds too slowly or not at all. The lower temperature feasible in practice, at which the reaction still proceeds adequately in a few hours, is about 60°C. Temperatures between 70 and 95°C are therefore generally preferred. In place of paraffin it is also possible to use other inert, high-boiling heat transfer agents, for example hydrophobic glycol ethers, such as the dibutyl ether of ethylene glycol, or also 1,2- or 1,3-dichlorobenzene or dibutyl ketones. The term paraffin also includes paraffin oils, which are marketed as high viscosity or low viscosity paraffin oils and the composition and properties of which are laid down in the DAB (German Pharmacopoeia).

Water must be present during the condensation reaction, since subsequent absorption of water, that is to say swelling of a resin prepared by a condensation reaction without the addition of water, proceeds too slowly and too incompletely.

Preferably, a 3 to 4 molar, especially 3.4 molar, pyrogallol solution is used. Formaldehyde is preferably used in the form of the customary commercial 37% strength aqueous solution.

The resin preferably used has a particle size of 100 to 200 mesh and should have a reversible minimum water content of 40% by weight, but preferably has a reversible water content of 45 to 50% by weight (determined by the loss in weight of the air-dried resin in the H⁺ form after heating at 110°C for 20 hours and then swelling the dried resin in 2N HCl for 48 hours). A lower water content lowers the exchange capacity. A water content higher than 70% results in mechanically unstable and relatively soluble resins, so that a water content of 40 to 60% for the particle size fraction of 100 to 200 mesh is preferred.

An addition of NaOH to the reaction medium results in a pH value of about 6.0—6.8. If the pH is adjusted to too high a value, this results in undesired increased solubility of the resin (pK_a pyrogallol=7). A strongly acid condensation reaction is also possible, but is less advantageous since the reaction then becomes too rapid and causes foaming of the reaction medium.

Since the freshly formed resin droplets have condensed at the surface and some of them stick together, especially when relatively small experimental batches are processed on a laboratory scale, it frequently proves appropriate to comminute the process product, prior to curing, by mechanical means, for example in a commercially available homogeniser such as is used for the homogenisation of tissue samples. The homogeniser treatment is carried out for about 5 to 15 minutes and preferably for about 10 minutes. If the process is carried out on a semi-industrial or industrial scale, when, because of better mixing, it is easier to control so as to produce comparatively small particle sizes, homogenisation is as a rule no longer necessary.

The resin droplets formed must still be cured and this is appropriately effected by heating the suspension of resin and paraffin for 15—25 hours and preferably for 20 hours at about 110—130°C and preferably at 115—120°C.

After complete curing, the hot heat transfer medium, for example paraffin, is filtered off and the resin is washed until it is free from paraffin. Organic solvents, such as chloroform and methanol are suitable as the wash liquid.

Coarser resin particles, for example 50 to 100 mesh, can also be used. However, the preferred smaller grain size of 100 to 200 mesh has the advantage that for given column dimensions and for a given amount of eluant, the amount of Ge-68 which appears in the Ge-68 eluate is about 40% less. Thus, if the same selectivity is to be achieved with resin particles with a particle size of 50—100 mesh, this demands larger columns and more eluant.

The exchanger resin of the selected particle size is suspended in warm water at about 60 to 70°C and the water is decanted off, this operation being repeated several times, after which the resin is appropriately brought into equilibrium with 2N HCl in order to prepare an ion exchanger which is ready for use. The resulting resin can be stored under 2N HCl or dry. It is not stable to alkali metal hydroxide solution.

If curing has been preceded by homogenisation, particles in dust form can be present and these are not easily removable by sieving and decanting. In this case, it proves appropriate to shake the resin for several hours, for example 5 hours in 2N HCl on a commercially available shaking apparatus, after which the liquid is decanted off, giving an ion exchanger ready for use.

The ion exchanger is filled into columns which, for carrying out laboratory experiments, have a diameter of about 0.5 to 1.5 cm and are filled to a height of about 5 to 6 cm with the ion exchanger.

Depending on the amount of exchanger resin used, loading with up to 20 mCi of Ge-68 can be carried out, incubation times of 5 to 24 hours being suitable for loading. The loading capacity is about 35 to 45 and as a rule about 40 mg of Ge/g of ion exchanger. The eluant used is appropriately a dilute HCl in a concentration of 2 to 5 normal, about 2 to 10 ml being used per elution, depending on the amount of resin employed. The flow rates achievable under normal pressure prove to be adequate and are about 2 ml/minute for a column diameter of about 1 cm.

The following distribution coefficients (CD) are achievable:

$$CD_{Ge} = \frac{\text{Ge-68 activity on the exchanger}}{\text{Ge-68 activity in the supernatant liquor}} = 2,000 \text{ to } 12,000$$

$$CD_{Ga} = \frac{\text{Ga-68 activity on the exchanger}}{\text{Ga-68 activity in the supernatant liquor}} = 0.05 \text{ to } 0.12$$

It proves advantageous that the time required for elution is short and of the order of magnitude of, for example, 3 to 5 minutes. Since the elution is preferably carried out with hydrochloric acid, the Ga-68 is in the ionic form and can easily be further processed. The eluate contains less than $3 \times 10^{-4}\%$ of Ge-68, relative to Ga-68, and is free from other metals. The yield of Ga-68 is $75 \pm 5\%$ and the elution can be repeated as often as desired.

The organic ion exchanger according to the invention thus possesses a high adsorption capacity for germanium and a low adsorption capacity for gallium, especially when a dilute HCl solution (2 to 5N) is used, and the eluate is free from complexing agents, for example EDTA, oxine or oxalate, which make further processing of Ga-68 to radiopharmaceutical agents more difficult.

The examples which follow are intended to illustrate the invention in more detail.

20 Example 1

Preparation of the Pyrogallol/Formaldehyde Ion Exchange Resin

About 700 ml of paraffin (viscous) were warmed to 85 to 90°C in a heating bath which was fitted with lateral baffle plates and a stirrer. A solution of 0.4 mol (50.4 g) of pyrogallol, 80 ml of H₂O, 48 ml of formaldehyde (37% strength) (0.44 mol) and 2 ml of 1N NaOH was added, whilst stirring vigorously. The resulting suspension was stirred for 1.5 hours at the indicated temperature. Fine resin droplets formed, the surface of which was already condensed and some of which stuck to one another. The batch was therefore comminuted for 10 minutes using a homogeniser such as is customarily used for homogenising tissue samples (commercial product "Ultraturrax"), after which final through-curing of the particles was effected by heating for 20 hours at 115 to 120°C.

After curing, the hot paraffin was filtered off and the resin was washed several times with chloroform and methanol until paraffin-free. It was then sieved, typical yields for a batch of this type being as follows:

	Particle size mm	U.S. mesh	Yield (g)
35	>0.3	50	27.6
	0.3—0.15	50—100	27.6
	0.15—0.075	100—200	5.0

The resin with a particle size of 0.15 to 0.075 mm was suspended in warm water at 60 to 70°C and the water was decanted off, this operation being repeated several times. The resin was equilibrated with 2N HCl. Particles in dust form which had formed as a result of the homogenisation and were difficult to separate off, were removed by shaking the resin for about 5 hours in 2N HCl on a shaking apparatus and then decanting off the acid. The resin was stored under 2N HCl. The loading capacity of the ion exchanger was 38 mg of germanium per g of exchanger. The reversible water content of the exchanger was 45%.

45 Example 2

Example 1 was repeated using the same amounts of the reactants, but the paraffin (viscous) was warmed to 65 to 70°C. The batch was stirred for 3 hours, and the same product as in Example 1 was then obtained and this was also worked up as described in Example 1.

50 Example 3

A test batch corresponding to Example 1, but with paraffin pre-heated to 103°C, gave the following result. The aqueous formaldehyde/pyrogallol solution could no longer be added all at once but had to be introduced in portions of about 10 ml at intervals over a period of 40 minutes, since after each addition of the reagent the batch foamed vigorously after a brief delay. After further stirring for

one hour at 103°C, a coarse-grained resin was obtained and this had to be subjected to a prolonged (25 minute) treatment in the homogeniser. The resulting ion exchanger displayed the same binding capacity towards germanium, but had a water content 10% lower than that of the product obtained by a condensation reaction at 85—90°C according to Example 1.

5 Example 4

The experimental conditions corresponded to those in Example 1, except that hot paraffin at 90°C was replaced by hot 1,2-dichlorobenzene (melting point -16.7°, boiling point 172.9°C, density 1.29 g/ml, non-combustible) at 90°C. In respect of the germanium-binding capacity and the water content, the product formed was identical to the ion exchanger prepared by the condensation reaction in paraffin. The yield of smaller particles was slightly higher.

Example 5

400 ml of dibutyl ketone (5-nonanone, melting point -5.9°C, boiling point 187°C, density 0.82 g/ml) were heated to 85°C and a solution of 25.2 g of pyrogallol, 40 ml of H₂O, 24 ml of 37% strength formaldehyde and 1 ml of 1N NaOH was added, whilst stirring vigorously. The batch was stirred for 1.5 hours at 85°C. After treatment in the homogeniser for 10 minutes and curing for 18 hours at 115°C, the yield in respect of the 100—200 mesh particle size was twice as high as that in the case of the resin prepared by the condensation reaction in paraffin; the germanium-bonding capacity and the water content were the same for the two resins. However, 5-nonanone has an intense odour and is about five times more expensive than paraffin or 1,2-dichlorobenzene.

20 Example 6

Use of the Ion Exchanger as a Ge-68/Ga-68 Nuclide Generator

The ion exchange resin from Example 1 was incubated with a 0.5N hydrochloric acid solution of carrier-free Ge-68 for 5 hours, 0.25 g of resin being loaded with 1 mCi of Ge-68.

The distribution coefficients were as follows:

$$\begin{array}{l} \text{Ge-68 activity on the exchanger} \\ \hline \text{Ge-68 activity in the supernatant liquor} \quad = 2,000 \\ \\ \text{Ga-68 activity on the exchanger} \\ \hline \text{Ga-68 activity in the supernatant liquor} \quad = 0.1 \end{array}$$

The resin was transferred to a chromatography column 0.5 cm in diameter, which was provided with a glass frit on the base and had already been filled with three times the amount (750 mg) of inactive resin (free from Ge-68) as the collecting layer (total fill height of the column 6.0 cm).

The resulting exchanger column was pre-rinsed with 50 ml of 2N HCl and was then ready for use; It proved appropriate to use a glass frit as the upper closure also, to prevent the resin whirling up when the eluant was added. The eluant used was hydrochloric acid of various normalities (2—5N) in an amount of 2.5 ml per elution.

To enable a statement to be made with regard to the operating life, generators described under Example 2 were subjected to long-term elution (5.5 l of HCl of various normalities (2—5N) were passed continuously through the resin bed at a flow rate of 0.29 ml/minute).

With this amount of HCl, irrespective of the normality used, only 0.09% of the Ge-68 initially adsorbed was eluted. However, migration of the Ge-68 from the incubated resin layer into the collecting layer did take place. On the basis of the speed of migration measured, it was calculated that break-through for the column (sudden rise in Ge-68 in the Ga-68 eluate) would take place after 12 to 15 l of hydrochloric acid had been passed through. This corresponds to 4,800—8,000 elutions. Under conditions likely to be encountered in practice 3—4 elution, with 2.5 ml in each case, per day and a flow rate of 0.7 ml/minute) an operating life of 1,600—2,000 elutions can be expected.

In the case of larger columns, which require 10 ml or more of eluant per elution, 5 N HCl is more advantageous as the eluant, since Ga-68 can be concentrated from this eluate simultaneously on a small column consisting of about 1 cm³ of a commercially available anion exchanger (quaternary ammonium groups incorporated in a matrix of styrene and divinylbenzene) and can then be eluted with small amounts of H₂O (3—4 ml).

Literature: K. A. Kraus and F. Nelson: Metal Separation by Anion Exchange. ASTM Spec. Techn. Publ. No. 195 (1958).

The enclosed graph shows the elution characteristics of a generator which was prepared in accordance with the instructions of Example 6 and was eluted about 60 times, with 2.5 ml of 2N HCl in each case, over a period of 100 days. The amount of pyrogallol washed out from the ion exchanger per elution was less than 10 µg (minimum lethal dose in dogs, administered intravenously, 80—100 mg/kg; H. M. Rauen, Biochemisches Taschenbuch (Biochemical Handbook), part II, Springer Verlag, 1964).

Claims

1. Ion exchanger for separating gallium-68 from its parent nuclide germanium-68, characterised in that it consists entirely or substantially of a condensation product obtained from polyhydroxybenzene having not less than 2 adjacent hydroxyl groups (ortho-position) and formaldehyde in a molar excess of 5 to 15%, or contains such a condensation product incorporated therein, and wherein the condensation product has a reversible moisture content of not less than 40% by weight. 5
2. Ion exchanger according to Claim 1, characterised in that pyrogallol (1,2,3-trihydroxybenzene) is preferably employed for the condensation reaction.
3. Ion exchanger according to Claim 1, characterised in that the molar excess of formaldehyde is about 10%. 10
4. Process for the preparation of the ion exchanger according to Claim 1, 2 or 3, characterised in that a polyhydroxybenzene having not less than 2 adjacent hydroxyl groups, or a mixture of such polyhydroxybenzenes, is subjected to a condensation reaction with formaldehyde in an excess of 5 to 15 mol %, in the presence of water, in a hot, hydrophobic medium, which is compatible with the reactants and is inert towards the latter, whilst stirring, the condensation product is cured, the hot inert medium is filtered off and the cured resin is washed until free from the inert medium and sieved. 15
5. Process according to Claim 4, characterised in that the hydroxybenzene used is pyrogallol in 3 to 4 molar and in particular 3.4 molar aqueous solution.
6. Process according to Claim 4 or 5, characterised in that formaldehyde is used in the form of the commercially available 37% strength aqueous formaldehyde solution. 20
7. Process according to Claim 4 or 5, characterised in that paraffin is used as the compatible and inert medium.
8. Process according to Claim 6, characterised in that when pyrogallol is used as the hydroxybenzene, the condensation reaction is carried out at 85 to 90°C. 25
9. Process according to one of Claims 4 to 7, characterised in that the condensation reaction is carried out at a slightly acid pH value, in particular at pH 6 to 6.8.
10. Process according to one of Claims 4 to 8, characterised in that the fresh condensation product is cured for 15 to 25 hours at 115 to 120°C.
11. Process according to Claim 9, characterised in that the condensation product is comminuted mechanically prior to curing. 30
12. Use of the ion exchanger according to Claim 1 for separating gallium-68 from its parent nuclide germanium-68 by exchanger chromatography.
13. Use according to Claim 12, the ion exchange resin having a particle size of about 0.15 to 0.075 mm. 35
14. An ion-exchanger for separating gallium-68 from its parent nuclide germanium-68, substantially as hereinbefore described with reference to the Examples.
15. A process for the preparation of an ion-exchanger substantially as hereinbefore described with reference to Examples 1 to 5.
16. Use of an ion-exchanger according to claim 1 for separating gallium-68 from germanium-68 substantially as hereinbefore described with reference to Example 6. 40